IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Mouritsen et al.
Serial No.	:	08/955,373
Filed	:	October 21, 1997
Examiner	:	Ron Schwadron
Art Unit	:	1644
For	:	**INDUCING ANTIBODY RESPONSE AGAINST SELF-PROTEINS WITH THE AID OF FOREIGN T-CELL EPITOPES**

745 Fifth Avenue, New York, New York 10151

DECLARATION OF BIRGER BORREGAARD, M.Sc., MBA

Commissioner for Patents
Washington, D.C. 20231
Dear Sir:

BIRGER BORREGAARD declares and says that:

1. I am the Chief Operating Officer of Pharmexa A/S (Pharmexa), and have held this position since about February 2000. Prior to being the COO of Pharmexa, I was the Director of Business Development with Pharmexa , a position I held from mid-1998, when I joined Pharmexa, to about February 2000, when I was promoted to COO of Pharmexa. In my position of COO of Pharmexa, I remain responsible for the Pharmexa's business development activities, and am authorized to speak on behalf of Pharmexa. Pharmexa is the assignee of the above-captioned application (the present application), by virtue of assignment from the inventors and a corporate name change (from M&E Biotech). I hold an M.Sc. in biology from University of Copenhagen and a Henley MBA. Prior to joining Pharmexa, I served as CEO of Dansk Biologisk Production AMBA, as Executive Assistant to the CSO at the State Serum Institute, Copenhagen, and have held various positions with Novo Nordisk A/S, including Business Development Manager. I serve as a member of the board of the commercial trust Henley MBA in Denmark and am a former chairman of the Henley Alumni Association - Denmark. From my education, training and experience, including my experience at Pharmexa, I am familiar with the subject matter of the present application, including that I am informed that a concurrently-filed Amendment presents claims as reproduced below or substantially as reproduced below, after my signature, which I have read and understood. Accordingly, I respectfully submit that I am well qualified to speak as to the present application, and particularly, success of the present invention,

such as the commercial success of the present invention, including licenses that have been granted and financing generated, and technical or art-recognized success, including trials and publications. I am advised that success, such as commercial success, of an invention is an indicia of patentability; and, I respectfully request that the success, including the commercial and technical or art-recognized success of the present invention be fully considered as demonstrating the patentability of the present invention. At Pharmexa, we proudly refer to the present invention as AutoVac™ technology; and, this term shall also be used herein.

A BRIEF HISTORY OF PHARMEXA – EARLY AND CONTINUOUS COMMERCIAL SUCCESS OF, AND RECOGNITION OF THE PLACE IN THE ART OCCUPIED BY, THE PRESENT INVENTION

2. a. In 1992, Pharmexa entered into a collaborative agreement with Ferring Pharmaceuticals A/S. The Ferring agreement was spurred by Pharmexa's discovery of the AutoVac™ technology. Thus, the early Ferring agreement was based upon the present invention, including its the unique position in the art as fulfilling an unmet need; and, demonstrates commercial success of the present invention. Also in 1992, the first general proof of principle for the AutoVac™ technology was obtained and the priority application of the present application was filed in 1993.

b. As to the present invention - AutoVac™ technology - wherein the self-protein is human TNF-alpha (the AutoVac™ TNF-alpha pharmaccine), successful animal results were published in Nature Biotechnology (Dalum et al. Vol 17, p666-669, July 1999) (copy included in Exhibit 1 – a collection of journal articles demonstrating success of the present invention), showing technical success and surprising superiority of the instant invention. And, in 1997, Pharmexa entered into a license agreement providing Ferring the global rights to all human therapeutic indications of the AutoVac™ TNF-alpha pharmaccine. This Ferring agreement was based also upon the present invention, including its the unique position in the art as fulfilling an unmet need; and, demonstrates commercial success of the present invention.

c. Pharmexa's first private placement of shares was successfully completed in May 1997, contributing net proceeds to the Company of DKK 75 million. Subsequent to the private placement Pharmexa obtained loan financing from Business Development Finance totalling DKK 21 million. This level of financing was based also upon the present invention, including its the unique position in the art as fulfilling an unmet need.

d. A second private placement took place in June 1999, providing net proceeds to Pharmexa of DKK 31 million. This level of financing was based also upon the present invention, including its the unique position in the art as fulfilling an unmet need; and, this level of financing also demonstrates commercial success of the instant invention.

e. In March 2000, Pharmexa entered into a collaboration with Schering-Plough Animal Health (SPAH) regarding pharmaccines for veterinary use based on Pharmexa's AutoVac™ technology. On a global, exclusive basis Schering-Plough received a license for use of the AutoVac™ technology in the veterinary field. This SPAH agreement was based also upon the present invention, including its the unique position in the art as fulfilling an unmet need.

f. In April 2000, Pharmexa and Ferring announced the approval of the first clinical trial on cancer patients with the present invention - AutoVac™ technology - wherein the self-protein is human TNF-alpha and later that month Pharmexa entered into a research and development collaboration with H. Lundbeck regarding the use of the present invention - AutoVac™ technology as to neurodegenerative diseases. The approval of a clinical trial of an embodiment of the present invention indicates technical success of the present invention. The Lundbeck agreement was based also upon the present invention, including its the unique position in the art as fulfilling an unmet need; and, demonstrates commercial success of the present invention.

g. Late May 2000, Pharmexa was listed on the Copenhagen Stock Exchange, providing DKK 375 million in net proceeds, leading to a significant expansion of employees and activities. Thus, there was an Initial Public Offering (IPO) that raised more than DKK 375 million in net proceeds, based on the present invention, including its the unique position in the art as fulfilling an unmet need. This successful IPO demonstrates commercial success of the present invention. A copy of the May 31, 2000 press release - Offer of shares in M&E Biotech subscribed 3 times – is included in Exhibit 2, a collection of press releases.

h. During the autumn of 2000, Pharmexa achieved significant results with the present invention in various mouse models: An embodiment of the instant invention wherein the self-protein is HER-2 showed the ability to eliminate HER-2 positive tumors; Professor Paul Foster from Australia using an embodiment of the instant invention wherein the self-protein is IL-5 showed a complete remission of asthma in asthmatic mice; and Professor Tanaka at University of Tokyo using an embodiment of the instant invention wherein the self-protein is

RANKL confirmed significant reduction in bone loss in several models of osteoporosis. These results further illustrate the technical success and surprising superiority of the present invention.

PHARMEXA'S NUMEROUS COLLABORATIVE PARTNERS AS TO THE INSTANT INVENTION DEMONSTRATE COMMERCIAL SUCCESS

3. Pharmexa's collaborative partners as to the present invention include: Ferring; H. Lundbeck; Schering-Plough; and Lexigen/Merck KgaA. The agreements entered into with these and other partners is based on the present invention, including its unique position in the art as fulfilling an unmet need, and demonstrate commercial success of the present invention.

4. A brief description of some of Pharmexa's collaborative partners as to the instant invention is as follows:

a. Ferring Pharmaceuticals A/S: Ferring is a speciality, research-driven biopharmaceutical company active in the global market. The company identifies, develops and markets innovative products in the fields of urology, gynaecology, gastroenterology and endocrinology. In recent years, Ferring has expanded beyond its traditional European base. The company now has marketing presence in over 40 countries employing more than 2,000 employees, with revenues in the year 2000 of more than 400 million Euros. As mentioned above, Pharmexa entered into a licensing agreement with Ferring in April 1997, and under separate agreements Ferring pays certain the costs involved with the program which is a subject of the license, and Pharmexa acts as consultants for Ferring during the pre-clinical and clinical development and in the event of future sublicensing. These agreements are based on the present invention, including its the unique position in the art as fulfilling an unmet need, and demonstrate commercial success of the present invention.

b. H. Lundbeck A/S: H. Lundbeck is an international pharmaceutical company engaged in the research and development, production, marketing and sale of drugs for the treatment of psychiatric and neurological diseases. In 2000 the consolidated net turnover was DKK 5.6 billion and the number of employees approximately 3,000 people. As mentioned above, H. Lundbeck and Pharmexa entered into an agreement as to the instant invention which gives H. Lundbeck a specific global exclusive license. Pursuant to the agreement, H. Lundbeck pays all expenses related to the program which is the subject of the license, and H. Lundbeck paid a down-payment to Pharmexa. Furthermore, depending on results obtained, H. Lundbeck

can pay Pharmexa as to its license pertaining to the present invention, total milestone payments of approximately DKK 150 million over the entire duration of the project. Pharmexa will also receive royalties on the sale of final products. And, H. Lundbeck also invested DKK 10 million in connection with Pharmexa's IPO on the Copenhagen Stock Exchange. This agreement and investment is based on the instant invention, including its the unique position in the art as fulfilling an unmet need, and demonstrate commercial success of the present invention. An April 17, 2000 press release - M&E Biotech A/S and H. Lundbeck A/S enter into a research and development agreement – is included in Exhibit 2.

c. Schering-Plough Animal Health (SPAH): SPAH is the worldwide animal health business of Schering-Plough Corporation, U.S.A., a research-based company engaged in the discovery, development, manufacturing and marketing of pharmaceutical products worldwide. As mentioned above, Pharmexa and Schering-Plough Animal Health (New Jersey, USA) entered into a license agreement regarding the present invention. On a world-wide and exclusive basis Schering-Plough has been given a license to the present invention for all uses in the veterinary field. Schering-Plough pays all research, development, manufacturing and marketing costs. Schering-Plough has paid to Pharmexa a technology transfer fee and will pay up-front and milestone payments on each product. Pharmexa will eventually also receive a royalty of Schering-Plough's net profit from product sales. Included in Exhibit 2 are press releases - M&E Biotech licenses AutoVac™ Technology to Schering-Plough Animal Health, and, Positive change in Pharmexa's collaboration with Schering-Plough Animal Health. This agreement is based on the present invention, including its the unique position in the art as fulfilling an unmet need, and demonstrates commercial success of the present invention.

d. Lexigen/Merck KgaA: Lexigen Pharmaceuticals, Corp., a subsidiary of Merck KGaA of Darmstadt, Germany, located in Lexington, Massachusetts, took an option as to a cancer embodiment of the present invention, as shown by the December 17, 2001 press release - Pharmexa announces AutoVac™ cancer license option – included in Exhibit 2. This agreement is also based on the present invention, including its the unique position in the art as fulfilling an unmet need, and demonstrates commercial success of the present invention.

LITERATURE DEMONSTRATING SUCCESSAND ART RECOGNITION OF THE INSTANT INVENTION

5. Literature demonstrating the technical success of the instant invention in Exhibit 1 includes:

Hertz, M., Juji, T., Tanaka, S. & Mouritsen, S. A therapeutic RANKL vaccine induces neutralizing anti-RANKL antibodies and prevents bone loss in ovariectomized mice. *23rd Annual Meeting American Society of Bone and Mineral Research*, 12–16 October 2001, Phoenix, AZ, USA, **Abstract 1043**, (2001).

Hertz,M. et al. Active Vaccination Against IL-5 Bypasses Immunological Tolerance and Ameliorates Experimental Asthma. *J Immunol* **167**, 3792-3799 (2001).

Hertz,M., Mouritsen,S.; Gautam,A. Emerging therapeutic vaccines. *Drug Discovery World* **Summer 2000**, 49-53 (2001).

Dalum,I. et al. Therapeutic antibodies elicited by immunization against TNF-alpha. *Nat Biotechnol* **17**, 666-669 (1999).

Dalum,I. et al. Induction of cross-reactive antibodies against a self protein by immunization with a modified self protein containing a foreign T helper epitope. *Mol Immunol* **34**, 1113-1120 (1997).

These publications and the results reported therein demonstrate success and art-recognition of the instant invention.

PHARMEXA'S NUMEROUS PROGRAMS RESULTS, PARTNERS AND COLLABORATIONS DEMONSTRATE SUCCESS AND ART RECOGNITION OF THE INSTANT INVENTION

6. Programs in various stages involving embodiments of the instant invention include:

Indication	Name	Target	Status	Partner
Breast cancer	ME103	HER-2 DNA	Phase I/II	
Breast cancer	ME104	HER-2 Protein	Late Pre-Clinical	
Asthma	ME105	IL5	Pre-clinical	
Osteoporosis	ME107	RANKL	Research	
Allergy	ME108	IgE	Research	
Neurodegenerative disorder	ME106	Not Disclosed	Research	Lundbeck
Veterinary conditions		Not Disclosed	Target Species	Schering-Plough
Cancer		Not Disclosed	Research	Lexigen/Merck KGaA

Note also press releases in Exhibit 2, including:

September 24, 2001: Pharmexa initiates phase I/II trial in breast cancer in the United Kingdom.

September 20, 2001: Pharmexa publishes important pre-clinical data in its AutoVac™ IL5 asthma programme.

July 9, 2001: Pharmexa initiates phase I/II trials in breast cancer in Denmark .

August 1, 2001: Pharmexa presents important pre-clinical data in its AutoVac™ HER-2 breast cancer programme.

April 12, 2002: Pharmexa announces that GlaxoSmithKline has exclusive option on HER-2 Protein Breast Cancer project.

These programs, results, and collaborations demonstrate success and art-recognition of the instant invention.

CORRESONDING FOREIGN PATENTS HAVE BEEN GRANTED AND TECHNICAL AND PATENT PROFESSIONALS MUST HAVE FAVORABLY EVALUATED THE PRESENT INVENTION

7. As yet a further indicia of patentability, it is noted that while the USPTO is not bound by decisions of foreign patent offices, nonetheless, foreign patents corresponding to the present application have been granted as indicated in Exhibit 3, over art as cited against the present application, showing that others skilled in the art and in the patent field have recognized the patentability of the present invention (e.g., Examiners in foreign patent offices). And, on this point, it is noted that it is not uncommon for an entity to study both a technology and the patentability of the technology before entering into an agreement with respect thereto – this is

commonly called "due diligence" and can involve technical and patent professionals. It is likewise not uncommon for an entity or an individual to reseach a company's technology and the patentability thereof before investing in the company – also called "due diligence" and can involve technical and patent professionals. The many entities have entered into agreements concerning the instant invention and the many that have invested in Pharmexa and hence the instant invention, demonstrate that others skilled in the art and in the patent field have recognized the patentability of the present invention. Simply, the many entities have entered into agreements concerning the instant invention and the many that have invested in Pharmexa and hence the instant invention, as well as the grant of foreign patents, demonstrates that technical and patent professionals must have favorably evaluated the present invention and particularly its position in the art and its patentability.

CLEAR AND CONVINCING EVIDENCE OF COMMERCIAL SUCCESS, TECHNICAL SUCCESS, ART RECOGNITION, AND PATENTABILITY OF THE INSTANT INVENTION HAS BEEN PROVIDED

8. I respectfully submit that the foregoing provides, *inter alia*, clear and convincing evidence of the commercial success, technical success, art recognition and patentability of the present invention: Clearly, many entities have entered into agreements concerning the instant invention; many have invested in the instant invention; many successful results of embodiments of the instant invention have been reported; clinical and pre-clinical trials of embodiments of the instant invention are underway; and foreign patent offices have recognized the patentability of the instant invention; *inter alia*. Indeed, it is also noted that the many employed as a result of the instant invention - directly by Pharmexa and indirectly by collaborators who work with respect to embodiments of the instant invention – further demonstrate investment and proceeds spent as to the present invention and thereby further demonstrate commercial success. Hence, I respectfully submit that I have provided, *inter alia*, clear and convincing evidence of the commercial success, technical success, art recognition and patentability of the present invention.

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 17 May 2002 By: Birger Borregaard
BIRGER BORREGAARD, M.Sc., MBA

CLAIMS UNDERSTOOD TO BE ADDED OR SUBSTANTIALLY ADDED

--56. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein;

whereby, the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

57. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

58. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that

animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

59. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

60. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

61. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

62. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

63. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

64. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

65. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that

animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

66. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

67. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

68. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

69. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

70. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

a. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein;

whereby, the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

b. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide

containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

c. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

d. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

e. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

f. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

g. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

h. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

i. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

j. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution

preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

k. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

l. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

m. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

n. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken.

71. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, inducing antibody production in the animal against the self-protein of that animal, and eliciting an immune response in the animal which includes an MHC class II immune response as to an immunodominant T-cell epitope which is foreign to the animal and an autoantibody response in other MHC-haplotypes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

a. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing the immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or

b. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing the immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

72. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

a. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein;

whereby, the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

b. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

c. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said

substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

d. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

e. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

f. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

g. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

h. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier

protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

i. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

j. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

k. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide

containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

l. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

m. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

n. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken.

73. (New) The method of any one of claims 56-72 wherein the modified self-protein is a recombinant modified self-protein.

74. (New) The method of any one of claims 56-72 wherein the self-protein is tumor necrosis factor alpha (TNF-α), tumor nucrosis factor beta (TNF-β), gamma interferon (γ-interferon), interleukin 1 (IL-1) or immune globulin (IgE).

75. (New) The method of claim 73 wherein the self-protein is tumor necrosis factor alpha (TNF-α), tumor nucrosis factor beta (TNF-β), gamma interferon (γ-interferon), interleukin 1 (IL-1) or immune globulin (IgE).

76. (New) The method of any one of claims 56-72 wherein the administering includes administering an adjuvant.

77. (New) The method of claim 76 wherein the adjuvant comprises calcium phosphate, saponin, quil A or a biodegradable polymer.

78. (New) The method of claim 73 wherein the administering includes an adjuvant.

79. (New) The method of claim 75 wherein the administering includes an adjuvant.--